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EXAMINER	
PANDE, SUCHIRA	
ART UNIT	**PAPER NUMBER**
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/723,520	ANDERSEN ET AL.	
	Examiner	Art Unit	
	Suchira Pande	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-30,32,43 and 44* is/are pending in the application.

4a) Of the above claim(s) *10-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6, 8-9, 19-30, 32, 43-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/28/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

CLAIM STATUS

1. Examiner acknowledges the amendment filed on July 19, 2007. Applicant has amended claims 1, 4, 8-9, 19-25, 43; cancelled claims7, 31, 33-42; added new claim 44 and withdrew claims 10-18. Consequently claims 1-6, 8-9, 19-30, 32, 43-44 are currently pending and will be examined in this action.

Specification

2. Amendments to specification filed on July 19, 2007 address the issues related to cross-referencing and use of trademarks. Hence the objections with respect to these aspects raised in earlier office action are withdrawn.

Response to claim amendments

112 rejections of claims 22 and 23

3. Amendment to claim language of claims 22 and 23 render the rejection of above two claims 35 U.S.C. 112, second paragraph moot. Hence this rejection is being withdrawn.

102 (b) rejections of claims 1-2, 4-9, and 43 over Heid et al.; and claims 1-4,19-28, 32-35 and 37-39 over Dolganov et al.

4. Amendment to claim language of independent claims 1 and 19 render the 102 (b) rejections of claims over Heid et al. or over Dolganov et al. moot. Hence the102 (b) rejection of claims 1-2, 4-9, and 43 over Heid et al.; and claims 1-4,19-28, 32-35 and 37-39 over Dolganov et al. are being withdrawn.

103 (a) rejections of claims 29-31, 40-42 over Dolganov et al. in view of Heid et al.

5. Since the primary reference Dolganov et al. is withdrawn, corresponding 103 (a) rejections of claims 29-31, 40-42 using this primary reference is also withdrawn.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 1-2, 4-6, 8-9, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Heid et al. (1996) Genome Research 6: 986-994 in view of Ohnishi et al. (2001) J. Hum Genet 46:471-477 and First et al. (US Pat. 5,776,682 issued July 7, 1998).

Regarding claim 1, Heid et al. teach : A method for quantifying the expression of target gene sequences of interest in a sample (see title and whole article), comprising the steps of:

(i) amplifying one or more cDNA molecules derived from a sample by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest (see page 993 par. 2 section Amplification of Target DNA and detection of Amplicon factor VIII),

and in the presence of at least one oligonucleotide probe complementary to a region of an amplified target gene sequence(see page 987 par. 3 where hybridization probe is taught) ,

said at least one oligonucleotide probe optionally labeled with a labeling system suitable for monitoring the amplification reaction as a function of time (see page 987 par. 3 where real time monitoring-- monitoring the amplification reaction as a function of time—using dual –labeled fluorogenic hybridization probe labeled with FAM and TAMRA is taught), and

(ii) quantifying the target gene sequences amplified in step (i) (see page 987 par. 4 results section).

Regarding claim 2, Heid et al. teaches a method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more cDNA molecules is obtained from mRNA derived from the sample (see page 986 par. 2-3 where reverse transcriptase RT-PCR is taught) .

Regarding claim 4, Heid et al. teaches a method in which said quantifying comprises analysis by real-time polymerase chain reaction amplification (see page 986 abstract line 1).

Regarding claim 5, Heid et al. teaches a method in which the polymerase chain reaction of step (i) is carried out for a number of cycles such that the amplification remains in the linear range (see page 988 figure 1 panel A where amplification in linear range is taught).

Regarding claim 6, Heid et al. teaches a method in which the amplification in step (i) is achieved with a thermostable DNA polymerase (see page 993 par. 3 where thermostable Taq DNA polymerase is taught).

Regarding claim 8, Heid et al. teaches a method in which the label is a fluorophore (see page 987 par. 3 where FAM a fluorophore is taught as label).

Regarding claim 9, Heid et al. teaches a method in which said at least one oligonucleotide probe is 5'-exonuclease probes (see page 987 par. 3-4 where 5'-Taqman exonuclease probes that are based on 5' nuclease activity of Taq polymerase are taught).

Regarding claim 43, Heid et al. teaches method of claim 1 in which the amplification is carried out in the presence of uracil N-glycosylase (see page 993 par. 3 where AmpErase uracil N-glycosylase is taught).

Regarding claim 44, Heid et al teach a method in which amplifying the cDNA molecules comprises as many as fourteen PCR cycles (see page 993 par. 4 where 40 PCR cycles are taught, by this teaching Heid et al teach a method comprising as many as fourteen PCR cycles).

Regarding claim 1, Heid et al. do not teach:

(i) amplifying ninety-five to one-thousand and thirteen molecules derived from a sample by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest, and in the presence of ninety-five to one-thousand and thirteen oligonucleotide probes complementary to a region of an amplified target gene sequence, said ninety-five to one-thousand and thirteen oligonucleotides probes labeled with a labeling system suitable for monitoring the amplification reaction as a function of time, each of which is complementary to a reqion of a different amplified target ,qene sequence of interest, and (ii) quantifying the target gene sequences amplified in step (i) wherein the amplifyinq of step (i) comprises ninety-five to one-thousand and thirteen PCR primer pairs, wherein each primer of the ninety-five to one-thousand and thirteen PCR primer pairs is present at a concentration of 30-45 picomolar.

Regarding claim 44, Heid et al do not teach amplifying the ninety-five to one thousand and thirteen cDNA molecules.

Regarding claims 1 and 44, Ohnishi et al. (see abstract) teach use of 200 primers (100 primer pairs) in a multiplex PCR reaction to amplify 100 genomic DNA fragments each containing a different amplified target qene sequence of interest (namely a SNP). Thus by teaching amplification of 100 samples, Ohnishi et al. teach amplifying ninety-five to one-thousand and thirteen molecules (since 100 samples taught by Ohnishi falls in the middle of the range recited in the instant claim) derived from a sample by polymerase chain reaction in the

presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest. Ohnishi et al. teaches use of allele specific probes that are labeled with FAM or VIC (see page 472, par. 3). By this teaching Ohnishi teaches 100 labeled oligonucleotides probes each of which is complementary to a region of a different amplified target gene sequence of interest. Ohnishi et al. teaches 100 primer pairs (see pages 473-474 table 1). Thus teaching (i) wherein the amplifying of step (i) comprises ninety-five to one-thousand and thirteen PCR primer pairs, wherein each primer of the ninety-five to one-thousand and thirteen PCR primer pairs.

Regarding claim 1, Ohnishi et al. teaches each primer pair is present at a concentration of 50 picomol (see page 471 par. 2).

Regarding claim 1, Ohnishi et al. do not teach each primer pair is present at a concentration of 30-45 picomolar (see page 471 par. 2).

Regarding claim 1, First et al. teach use of primer pairs in the concentration of 30-45 picomolar in multiplex PCR reactions (see Table 2 where preferred primer concentrations are taught. See primer pairs identified by SEQ ID 5 and 6 where 35 pM conc is taught; SEQ ID 21 and SEQ ID 22, SEQ ID 23 and 24 are used at 36.5 pM each; SEQ ID 97 and 98 are used at 44.5 pM each).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Ohnishi et al. and First et al. in the method of Heid et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill by both Ohnishi et al. and First et al.

Ohnishi et al. state " To reduce the amount of DNA required to less than 1ng for the assay of a single SNP and to make genome wide-association studies feasible, we combined a multiplex PCR method with the invader assay" (see page 471 par. 3). " The reproducibility and universality of the method was confirmed with two additional sets of 100 SNPs. Because we used 40 ng of --- DNA as a template for multiplex PCR, the amount needed to assay one SNP was only 0.4 ng." (see abstract last part). This teaching explicitly tells one of ordinary skill that by using the multiplexing method of Ohnishi et al. in the method of Heid et al. miniscule amounts of mRNA containing a gene of interest would be suffice as starting material from which cDNA could be made and quantified using this method.

First et al. state "it must be noted that these primer concentrations are the preferred concentrations. Variations maybe made in the concentration of the various primer concentrations to optimize PCR" (see col. 18, lines 25-27). Thus, an ordinary practitioner would have recognized that the primer concentration could be adjusted down to 30-45 pM each from the 50 pM each taught by Ohnishi et al. to maximize the desired results.

As noted in *In re Aller*, 105 USPQ 233 at 235,

> More particularly, where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.

Routine optimization is not considered inventive and no evidence has been presented that the selection of specific primer concentrations for amplification

was other than routine, that the products resulting from the optimization have any unexpected properties, or that the results should be considered unexpected in any way as compared to the closest prior art.

9. Claims 1-4,19-28 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dolganov et al. (2001) Genome Research 11:1473-1483 in view First et al. (US Pat. 5,776,682 issued July 7, 1998).

Regarding claim 1, Dolganov et al. teaches a method for quantifying the expression of target gene sequences of interest in a sample (see page 1473, par. 2 where real time PCR quantification is taught), comprising the steps of:

(i) amplifying ninety-five to one-thousand and thirteen cDNA (see page 1473, par. 1 where a two step process incorporating multiplex PCR (typically with a mix of 100 –300 gene specific primer sets) followed by real time PCR on generated cDNA product is taught, thus by teaching 300 cDNA amplification Dolganov et al. teach amplifying ninety-five to one-thousand and thirteen cDNA (as 300 cDNAs and corresponding nested primer sets and probes taught by Dolganov et al. falls within the range recited in the instant claims) molecules derived from a sample by polymerase chain reaction in the presence of a plurality of amplification primer sets suitable for amplifying target gene sequence of interest, and in the presence of ninety-five to one-thousand and thirteen oligonucleotide probes complementary to a region of an amplified target gene sequence, said ninety-five to one-thousand and thirteen oligonucleotide probes labeled with a labeling system suitable for monitoring the amplification reaction

as a function of time each of which is complementary to a region of a different amplified target gene sequence of interest (See par. 2 where real time amplification PCR using 200 gene-specific primers is taught this inherently involves use of a labled probe labeled with a labeling system suitable for monitoring the amplification reaction as a function of time) (Also see page 1474, par. 1 and Fig. 1 where RT-PCR for 34 genes was performed. Taqman hybridization probe is taught here which inherently indicates that it is complementary to a region of a different amplified target gene sequence. Taqman probe has fluorescein reporter dye at 5' end (FAM)). This along with the teaching above that Taqman primers and probes are used inherently teaches that probe used is complementary to a region of a different amplified target gene sequence of interest, and

(ii) quantifying the target gene sequences amplified in step (Gene quantification via real time PCR using nested Taqman primers is taught see legend of fig. 1) .

(i) wherein the amplifying of step (i) comprises ninety-five to one-thousand and thirteen PCR primer pairs (see above),

(ii) quantifying the target gene sequences amplified in step (i) (Gene quantification via real time PCR using nested Taqman primers is taught see legend of fig. 1) .

Regarding claim 1, Dolganov et al. do not teach wherein each primer of the PCR primer pairs is present at a concentration of 30-45 picomolar.

Regarding claim 1, Regarding claim 1, First et al. teach use of primer pairs in the concentration of 30-45 picomolar in multiplex PCR reactions (see Table 2 where preferred primer concentrations are taught. See primer pairs identified by SEQ ID 5 and 6 where 35 pM conc is taught; SEQ ID 21 and SEQ ID 22, SEQ ID 23 and 24 are used at 36.5 pM each; SEQ ID 97 and 98 are used at 44.5 pM each).

Regarding claim 19, Dolganov et al. teaches a method for determining a gene expression profile in a sample (see title), comprising the steps of:
(i) amplifying ninety-five to one-thousand and thirteen cDNA (see page 1473, par. 1 where a two step process incorporating multiplex PCR (typically with a mix of 100 –300 gene specific primer sets) followed by real time PCR on generated cDNA product is taught, thus by teaching 300 cDNA amplification Dolganov et al. teach amplifying ninety-five to one-thousand and thirteen cDNA (as 300 cDNAs and corresponding nested primer sets and probes taught by Dolganov et al. falls within the range recited in the instant claims) molecules derived from a sample by polymerase chain reaction in the presence of ninety-five to one-thousand and thirteen amplification primer sets suitable for amplifying the ninety-five to one-thousand and thirteen amplified target gene sequences of interest;

(ii) identifying the ninety-five to one-thousand and thirteen (see aabove) amplified target gene sequences having an observed efficiency of amplification greater than a selected level (see figs. 2 & 3 where amplification above a chosen threshold C_T is taught); and

(iii) quantifying the target gene sequences identified in step (ii) to obtain a gene expression profile (see page 1474 par. 1 and Fig. 1 where transcriptional profiling for 34 genes of varying abundance was performed using RT-PCR).

Regarding claim 19, Dolganov et al. do not teach wherein each primer of the PCR primer pairs is present at a concentration of 30-45 picomolar.

Regarding claim 19, First et al. teach use of primer pairs in the concentration of 30-45 picomolar in multiplex PCR reactions (see Table 2 where preferred primer concentrations are taught. See primer pairs identified by SEQ ID 5 and 6 where 35 pM conc is taught; SEQ ID 21 and SEQ ID 22, SEQ ID 23 and 24 are used at 36.5 pM each; SEQ ID 97 and 98 are used at 44.5 pM each).

Regarding claims 2 & 20, Dolganov et al. teaches generating RT-PCR for 34 genes as described above for claims 1&19 therefore it inherently teaches a method in which the amplification of step (i) is further carried out in the presence of a reverse transcriptase such that the polymerase chain reaction is reverse-transcription polymerase chain reaction and wherein the one or more cDNA molecules is obtained from mRNA derived from the sample.

Regarding claims 3 & 21, Dolganov et al. teaches a method in which the one or more cDNA molecules comprise a cDNA library (see page 1474 where 34 genes of varying abundance in the sample were reverse transcribed and the RT-PCR products were cloned into pCRII-TOPO vector is taught. Thus Dolganov et al. teaches a cDNA library).

Regarding claims 4 & 24, Dolganov et al. teaches said quantifying comprises analysis by real-time polymerase chain reaction amplification (see

page 1473 abstract where gene quantification via real-time PCR-based method is taught).

Regarding claim 25, Dolganov et al. teaches a method in which the amplifying in step (i) is further carried out in the presence of an oligonucleotide probe complementary to a region of an amplified target gene sequence of interest, said probe being labeled with a labeling system suitable for monitoring the amplification reaction in step (i) as a function of time (see page 1474, par. 1 and Fig. 1 where RT-PCR for 34 genes was performed. Taqman hybridization probe is taught here which inherently indicates that it is complementary to a region of an amplified target gene sequence. Taqman probe has fluorescein reporter dye at 5' end (FAM) which is suitable for real time detection see legend of fig. 1).

Regarding claim 26, Dolganov et al. teaches a method in which the product of step (i) is divided into a plurality of aliquots and said quantifying in step (ii) is performed on said aliquots (see page 1474 par. 2).

Regarding claim 27, Dolganov et al. teaches a method in which step (ii) comprises amplifying the product in one or more separate aliquots by polymerase chain reaction in the presence of an amplification primer set suitable for amplifying one of the target sequences of the plurality (see page 1474 par. 2 and fig. 1 where multiplex RT-PCR is followed by real time PCR using nested primers on small aliquots of RT-PCR product is taught).

Regarding claim 28, Dolganov et al. teaches a method in which the sequences of the amplification primer sets of step (i) are the same as the

sequences of the amplification primer sets of step (ii) (see page 1475, par. 2 and Fig. 4 where GAPDH, interleukin IL-8 and IL-13 were quantified is step 1 gene specific primer sets are taught for RT PCR amplification and then aliquots of the cDNA produced were quantified by real time amplification using primers specific for the above 3 genes. No explicit statement is made that same primers were used but this teaching by Dolganov et al. indicates that same primer sets could certainly be used both of step (i) and (ii).

Regarding claim 32, Dolganov et al. teaches a method in which the polymerase chain reaction of step (i) is carried out for a number of cycles such that the amplification remains in the linear range (see page 1474 par. 3 bottom and fig. 2 and 3 where linear amplification is taught up to 25 cycles for most abundant message and 30 cycles for less abundant message).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of First et al. in the method of Dolganov et al. at the time the invention was made. The motivation to do so is provided to one of ordinary skill both by Dolganov et al. and First et al.

In the section relating to Real-Time PCR Dolganov et al. state "Typically, an equivalent of 2.5 fg to 10 pg of total RNA was used in 25 μl of universal Master Mix. All forward and reverse TaqMan primers were optimized" (see page 1481 last par.). Thus Dolganov et al. teach to one of ordinary skill that optimization is performed for all primers. They do not specifically state the parameters that are optimized and the range of values associated with them.

First et al. provide specific guidance to one of ordinary skill in the art by stating "it must be noted that these primer concentrations are the preferred concentrations. Variations maybe made in the concentration of the various primer concentrations to optimize PCR" (see col. 18, lines 25-27). Thus providing explicit guidance to one of ordinary skill that the range of concentrations taught by First et al. work well for the various primers used by them and the practitioner with an ordinary skill in the art may adjust the primer concentration down to as low 30-45 pM each in multiplex PCR reactions.

10. Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Dolganov et al. (2001) Genome Research 11:1473-1483 and First et al. (US Pat. 5,776,682 issued July 7, 1998) as applied to claim 19 above further in view of Wang et al. (1998) Science 280: page 1077-1082.

Regarding claims 22 & 23, Dolganov et al. teaches a method of claim 19. But do not teach wherein the observed efficiency of amplification is greater than 70% (claim 22) and the observed efficiency of amplification is greater than 90% (claim 23).

Regarding claims 22 & 23, Wang et al. teach a multiplexing PCR method wherein the observed efficiency of amplification is 96 % (see page 1080 par. 4 where 96% of the 512 loci assayed using multiplex PCR amplification were correctly read in 100% of individuals). Thus teaching wherein the observed efficiency of amplification is greater than 70% (claim 22) and the observed efficiency of amplification is greater than 90% (claim 23).

It would have been prima facie obvious to one of ordinary skill in the art to practice the method of Wang et al. in the method of Dolganov et al. at the time the invention was made, the motivation to do so is provided by Wang et al. who state " Prototype genotyping chips were developed that allow simultaneous genotyping of 500 SNPs. The results provide a characterization of human diversity at the nucleotide level and demonstrate the feasibility of large scale identification of human SNPs" (see page 1077 abstract last part). This teaching of Wang et al. provides indication to one of ordinary skill in the art that array based amplification methods that allow simultaneous detection of 500 or more target genes where the efficiency of the multiplexed PCR amplification is greater than 95% are available. This knowledge provides the motivation to develop similar multiplexed amplification methods that allow simultaneous detection of expression of 500 or more target genes where the efficiency of the multiplexed PCR amplification is greater than 95%. Such multiplexed methods with this level of efficiency enable development of chips that are useful diagnostic tools for disorders where expression levels of different mRNAs are indicative of disease state.

11. Claims 29-30, are rejected under 35 U.S.C. 103(a) as being unpatentable over Dolganov et al. and First et al. applied to claim 27above in view of Heid et al. (1996) Genome Research 6: 986-994.

Regarding claim 29, Dolganov et. al. teaches the method of claim 27 suitable for monitoring the amplification reaction as a function of time.

Regarding claim 29, Dolganov et. al. does not teach a method in which the amplifying in step (ii) is further carried out in the presence of a molecule that produces a detectable signal when bound to a double-stranded polynucleotide suitable for monitoring the amplification reaction as a function of time.

Regarding claim 29, Heid et al. teaches a method in which the amplifying in step (ii) is further carried out in the presence of a molecule that produces a detectable signal when bound to a double-stranded polynucleotide suitable for monitoring the amplification reaction as a function of time (see Heid et al. page 992 where intercalating dye ethidium bromide is taught as a molecule that produces a detectable signal when bound to a double-stranded polynucleotide suitable for monitoring the amplification reaction as a function of time).

Regarding claims 30, Heid et al. teaches a method in which the molecule is selected from the group consisting of an intercalating dye and a minor groove binding dye (see Heid et al. page 992 where intercalating dye ethidium bromide is taught as a molecule).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to practice the method of Heid et al. in the method of Dolganov et al. and First et al. The motivation to do so is provided by Heid et al. who state " we have developed a novel " real time" quantitative PCR method. The method measures PCR product accumulation through a dual-labeled fluorogenic probe (i.e., Taq Man Probe). This method provides very accurate and reproducible quantitation of gene copies. Unlike other quantitative PCR methods, real time PCR does not require post-PCR sample handling,

preventing potential PCR product carry-over contamination and resulting in much faster and higher throughput assays (see abstract)."

Conclusion

12. All claims under consideration 1-6, 8-9, 19-30, 32 and 43-44 are rejected over prior art.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suchira Pande whose telephone number is 571-272-9052. The examiner can normally be reached on 8:30 am -5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax

phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Suchira Pande
Examiner
Art Unit 1637

JEFFREY FREDMAN
PRIMARY EXAMINER